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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
10/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,561	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,14-21,30 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,14-21,30 and 35-39* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :August 7, 2007 and April 24, 2007.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed August 7, 2007.

Claims 1, 3, 14-21, 30, and 35 have been amended. New claims 36-39 are acknowledged.

Claims 1, 3, 14-21, 30, and 35-39 are pending in the instant application.

Claims 1, 3, 14-21, 30, and 35-39 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statement filed August 7, 2007 is acknowledged. It is noted that the Examiner has considered only the Abstract of EP 1144623 B1. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Applicant's information disclosure statement filed April 24, 2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Priority

It is noted that the instant application claims priority to a laundry list of U.S. Provisional Applications and pending U.S. Patent Applications. The reference should be updated to reflect applications for patents that are pending or that have been abandoned. It is further noted that the instant claims are drawn to a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human amyloid precursor protein (APP) RNA sequence comprising SEQ ID NO:1905, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% of the nucleotides in each of the sense and antisense strands of the chemically modified nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications.

The Examiner acknowledges that the instant application claims priority to a number of PCT and US Applications, which, in turn, claim the benefit of provisional application 60/363,124, filed March 11, 2002, for example.

The instant application has been afforded priority to June 19, 2006, which is the filing date of the instant application because support for the invention as now claimed cannot be found in any other PCT Application, any US Application, or Provisional Application 60/363,124. Specifically, support for a chemically modified nucleic acid molecule complementary to a human amyloid precursor protein (APP) RNA sequence comprising SEQ ID NO:1905, wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are

chemically modified with modifications independently selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications cannot be found.

In summary, Applicant does not receive the benefit of the any earlier filed application, including provision application 60/363/124 because the prior application does not provide adequate support for the claims of the instant application and thus Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. Applicants contend that the instant invention is entitled to a priority date of, for example, March 11, 2002, which is the filing date of the 60/363,124 application. While the provisional application 60/363,124 provides support for a chemically modified nucleic acid molecule complementary to a human amyloid precursor protein (APP) RNA sequence comprising SEQ ID NO:1905, the provisional application 60/363,124 does not provide support for the limitation wherein about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from 2'-O-methyl, 2'-deoxy-2-'fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications.

If Applicants believe that they are entitled to an earlier priority date, then Applicant must point, with particularity, to where such support can be found in the specification of the prior application(s).

Specification

In the previous Office Action mailed April 4, 2007, the specification was objected to under 35 U.S.C. 132(a) because it introduced new matter into the disclosure. **This objection is withdrawn** in view of Applicant's Amendment and Remarks filed August 7, 2007. Specifically, the Examiner is withdrawing this objection in view of Applicant's Amendment to the sequence listing to recite SEQ ID NO:1905 as a DNA sequence.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed April 4, 2007, claims 1, 3, 14-21, 30, and 35 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicant's Amendment to the claims filed April 27, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the sequence listing to recite SEQ ID NO:1905 as a DNA sequence.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed April 4, 2007, claims 1, 3, 14-21, 30, and 35 were rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession Number NM_000484 (submitted and made of record on Applicant's Information Disclosure Statements filed August 7, 2006 and December 8, 2006), in view of Coulson et al. (Brain Research, 1997 Vol. 770:72-80), Elbashir et al., The EMBO Journal, 2001

(submitted and made of record on Applicant's Information Disclosure Statement filed December 8, 2006), Matulic-Adamic et al. (US Patent No. 5,998,203), and/or Parrish et al., Molecular Cell, 2000 (submitted and made of record on Applicant's Information Disclosure Statement filed December 8, 2006). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed April 4, 2007. It is noted that this rejection is also applied to new claims 36-39.

Response to Arguments

In response to this rejection, Applicants argue that none of the reference, alone or in combination, make obvious the presently claimed double stranded nucleic acid constructs because the cited references do not teach or suggest all of the claim elements. This argument has been fully considered, but is not found persuasive because KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396).

Applicant also argue that antisense and ribozyme art, such as the disclosures of Coulson et al. and Matulic-Adamic, respectively are not analogous art to double stranded nucleic acid molecule technology and should not be the basis for an obviousness rejection. For example, Applicants argue that the antisense molecules taught by Coulson et al. and the ribozymes taught by Matulic-Adamic et al. function in very different ways from the molecules of the instant invention and therefore would have

anticipated that different structural features of nucleic acids would have been required for their activities. Applicants also argue that the antisense molecules taught by Coulson et al. and the ribozymes taught by Matulic-Adamic et al. are substantially single-stranded prior to interacting with their target, while the chemically modified double-stranded nucleic acid molecules of the invention are almost completely in a duplex form. Applicants contend that it is well known to those skilled in the art that single-stranded nucleic acid molecules are more susceptible to nuclease attack than are double-stranded nucleic acids.

This argument has been considered, but is not found persuasive because contrary to Applicant's argument, antisense and ribozyme art are indeed analogous to double stranded nucleic acid technology, such as siRNA technology, since independently antisense, ribozyme, and siRNA all have the same general purpose - to function as inhibitors of nucleic acid gene expression. This is evidenced by the reference of Scanlon, K. (Current Pharmaceutical Biotechnology, 2004 Vol. 5:415-420) where the author categorizes antisense, ribozyme, and siRNA as anti-gene molecules, which use anti-gene technology to illicit gene silencing effects (see entire article). Furthermore, Applicant is reminded that it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06. Therefore, it would be obvious to substitute a siRNA with a ribozyme, and vice versa. Similarly, it would be obvious to substitute an antisense oligonucleotide with a siRNA, and vice versa.

Applicants also argue that Parrish teaches long dsRNA molecules, and not chemically synthesized double stranded RNA molecules comprising 18 to 27 nucleotides of Applicant's invention. Applicants contend that the long dsRNA molecules of Parrish et al. are not analogous to the double stranded RNA molecules of the instant invention. This argument has been considered, but is not found persuasive because the long dsRNAs of Parrish et al. and the double stranded RNAs of Applicant's invention both have the same general purpose - to function as inhibitors of nucleic acid gene expression. As discussed *supra*, it is obvious to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

Applicants next argue that Elbashir teaches away from the use of highly modified double stranded nucleic acid constructs, such as 2'-deoxy and 2'-O-methyl modified constructs since extensive substitution with 2'-deoxy and 2'-O-methyl modifications abolishes RNAi. This argument has been fully considered, but is not found persuasive because while Elbashir et al. teach that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity, the instant claims do not recite any functional language. Therefore, the skilled artisan would have been motivated to incorporate highly modified substitutions/chemical modifications to a siRNA to determine overall RNAi activity. In view of this evidence, Elbashir do not teach away from the use of highly modified siRNA constructs, but instead, motivates the skilled artisan to incorporate extensive modifications to determine overall RNAi activity. Additionally, the teachings of Elbashir et al. clearly provide the

skilled artisan with an expectation of success since the reference explicitly teaches the successful design of complete substitution (e.g. 100%) of one or both siRNA strands by 2'-deoxy residues and 2'-O-methyl residues.

Applicants finally argue that, at the time the invention was made, it was thought that additional chemical modifications to double stranded nucleic acids such as siRNAs were unnecessary for effective RNAi activity, thus providing no reasonable expectation of success. This argument has been fully considered, but is not found persuasive because, first, there would be a reasonable expectation of success to make an extensively modified siRNA in view of the teachings of Elbashir et al. As discussed *supra*, Elbashir et al. teach that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues. While complete substitution may have abolished RNAi activity, Applicant is reminded that the instant claims do not recite any functional language. Therefore, the skilled artisan would have been motivated and expected success in incorporating extensive substitutions/chemical modifications to a siRNA to determine overall RNAi activity. In view of this evidence, Elbashir do not teach away from the use of highly modified siRNA constructs, but instead, motivates the skilled artisan to incorporate extensive modifications to determine overall RNAi activity. Second, the claims are broadly drawn to include, for example, ribozymes and moderately long dsRNAs that do not exceed 27 nucleotides in length. Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. Therefore, there would be a reasonable expectation of success to apply each of the claimed modifications to the double stranded nucleic acid structures of Matulic-Adamic

et al. because the chemistry was well known to one of ordinary skill in the art at the time the invention was made (see Elbashir et al., Parrish et al., and Matulic-Adamic et al.) and merely selecting combinations of such modifications is considered a design choice. Moreover, Applicant is directed to the Supreme Court's recent decision in *KSR. Int'l Co. v. Teleflex*, 127 S.Ct. 1727, (2007) which concluded that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."

In view of the previous Office Action mailed April 4, 2007, the evidence of record shows that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Applicant's Amendment necessitated the new ground of rejection presented below:

Claim Objections

Claim 20 is objected to because of the following informalities: Claim 20 contains two commas after the number 8. Appropriate correction is required.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

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tcg
October 25, 2007

/Sean McGarry/
Primary Examiner
AU 1635